REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks presented herein, are respectfully requested.

Claims 6-8 and 18-19 are amended, claims 1, 4, 9-10, 16-17 and 22 are cancelled, and claims 27-31 are added. Claims 20-21 are allowed. Claims 5 and 23-26 have been withdrawn from consideration by the Examiner as a result of the Restriction Requirement. Thus, claims 2-3, 6-8, 11-15, 18-21, and 27-31 are currently under examination.

Claims 6-7 and 18-19 have been amended to remove subject matter that has been withdrawn from further consideration by the Examiner pursuant to 37 C.F.R. § 1.142(b). Claims 6-8 have also been amended to recite that the oligonucleotide "binds specifically" to the target nucleic acid. Support for this amendment can be found in various places in the specification including, for example, at page 1, lines 23-26. Support for the amendment to claim 8 can be found in previous claim 8, claims 6 and 7, as well as at various places in the specification including, for example, at page 2, lines 1-6; page 1, lines 23-26; and page 3, lines 13-16.

New claims 27-29, which depend on claim 8, are directed to methods of treating breast cancer, glioma, and melanoma, respectively. Support for these claims can be found at various places in the specification including, for example, at page 8, lines 14-29 and page 11, lines 22-27. Support for new claims 30-31 can be found at various places in the specification including, for example, at claims 6, 7 and 20.

The 35 U.S.C. §112 Rejections of the Claims

The Examiner rejected claims 18 and 19 under 35 U.S.C. § 112, second paragraph, stating that there is insufficient antecedent basis for the limitation "the portion of the nucleic acid for the antioxidant enzyme." The amendment to claims 18 and 19 to recite "human manganese superoxide dismutase" moots the 35 U.S.C. § 112(2) rejection of these claims. Therefore, Applicants respectfully request withdrawal of this rejection.

The Examiner also rejected claims 8, 11-15, 18 and 19 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner alleged that the specification, while being enabling for treatment of breast cancer, does not reasonably provide enablement for treatment of any cancer using the claimed antisense oligonucleotides. The Examiner cited Church *et al.*, *Proc. Nat'l. Acad. Sci* 90:3113-117 (1993) as evidence of unpredictability in the art and alleged

the claimed methods would not work over the entirety of the claim breath. Applicants respectfully traverse this rejection.

The claims are directed to a method of treating a tumor comprising reducing antioxidant enzyme levels in a cell of the tumor by administering a therapeutically effective amount of an antisense nucleic acid having the recited structural features. The claims are supported by numerous working examples (see M.P.E.P. §2164.02 for a discussion of Working Example). For instance, Applicants demonstrated that the claimed method treats breast cancer tumors. Specifically, Applicants demonstrated that an antisense nucleic acid specific for a manganese superoxide dismutase (MnSOD) nucleic acid reduced expression of MnSOD in a breast cancer cell, decreased clonicity of these cancer cells, and increased the percentage of tumor-free animals among those receiving grafts of breast cancer cells. See, for example, page 8, lines 22-29 and page 9, lines 26-31. Applicants have also demonstrated the correlation between reduced expression of MnSOD and clonicity in human melanoma. Specifically, Applicants demonstrated that 1 μM of an antisense oligonucleotide directed against human MnSOD decreased the clonogenic survival of human melanoma cells by 80 % (the same antisense nucleic acid decreased clonogenic survival of breast cancer cells by 90 %). See page 11, lines 3-27. Applicants have also demonstrated that the antisense nucleic acid of the invention has the same effect of reducing MnSOD protein expression and enzyme activity in glioma cells as in breast cancer cells. Therefore, Applicants have provided working examples for breast cancer, glioma and melanoma.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) (quoted in M.P.E.P. § 2164.01). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976) (cited in M.P.E.P. § 2164.01). The Examiner has stated that the level of one of ordinary skill in the instant art is high. And given the amount of direction provided by Applicant's disclosure, which includes the recited antisense nucleic acid and the mouse xenograft model, as well as the existence of the numerous

working examples discussed above, Applicants submit that any experimentation required to practice the claimed invention is not undue.

In addition, the Church *et al.* disclosure cannot indicate unpredictability in practicing the instant invention. The subject matter of the Church *et al.* disclosure differs significantly from Applicants' claimed invention, and therefore, Church *et al.*'s findings are irrelevant to Applicants' invention. For example, Church *et al.*'s tumor cells differ fundamentally from Applicants' cells. Applicants' tumor cells express MnSOD, while Church *et al.*'s tumor cells have little steady-state MnSOD expression of any sense MnSOD RNA species. See page 3115, right column. Since Church *et al.*'s tumor cells differ fundamentally from Applicants' tumor cells, the findings of Church *et al.* are irrelevant to Applicants' invention. Moreover, not only are the tumor cells different, Applicants' invention concerns the use of an antisense nucleic acid specific for human MnSOD to reduce expression of human MnSOD, while Church *et al.* expressed full-length cDNA encoding MnSOD. See page 3113, left column. The differences between Applicants' invention and the subject matter disclosed by Church *et al.* prevent any meaningful comparison of their respective results. In short, the Church *et al.* disclosure in inapposite cannot indicate unpredictability in practicing Applicants' claimed invention.

Accordingly, Applicants respectfully submit that claims 8, 11-15, 18 and 19 are fully enabled and request the Examiner reconsider and withdraw the 35 U.S.C. § 112, first paragraph, rejection of these claims.

The 35 U.S.C. § 102 Rejection of the Claims

The Examiner rejected claims 2-3, 6-7 and 22 under 35 U.S.C. § 102(b) as being anticipated by Kinscherf *et al.*, FASEB J. 12:461-467 (1998). In particular the Examiner alleges that Kinscherf *et al.* teach an antisense nucleic acid sequence containing phosphorothioate linkages that is 22 nucleotides in length and is 100 % complementary to the start codon of the nucleic acid encoding the human manganese superoxide dismutase. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Claims 6 and 7 are directed to oligonucleotides comprising an antisense nucleic acid sequence that is about 18 to 26 nucleotides in length, is at least 90% or 100 % complementary to and is capable of specifically binding to a contiguous portion of a nucleic acid that encodes a

human manganese superoxide dismutase; wherein the contiguous portion includes the start codon of the nucleic acid encoding the manganese superoxide dismutase. Claims 2-3 depend from claims 6 and 7.

Kinscherf *et al.* disclose on page 462, second column, first paragraph, a 22-mer having the sequence of CACGCCGCCCGACACAACATTG. This sequence is not at least 90 %, let alone 100 %, complementary to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase, wherein the contiguous portion includes the start codon of the nucleic acid encoding the manganese superoxide dismutase. The attached Exhibit A shows an alignment of the human manganese sequence with the Kinscherf *et al.* sequence. The start codon is bolded, while the six positions of mismatched are underlined. A 90 % complementary sequence would have no more than 2 mismatched positions in the 22 nucleotide sequence. The Kinscherf *et al.* sequence has 6 mismatched positions. Therefore, the antisense oligonucleotide of Kinscherf *et al.* does not anticipate claims 6-7, or their dependent claims (claims 2-3).

Accordingly, the Kinscherf *et al.* disclosure does not anticipate the claimed oligonucleotides, and Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 373-6913 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

LARRY W. OBERLEY *ET AL.*,

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6913

Date February 23, 2007

By W. Thai
Wendy Thai, Ph.D., J.D.
Reg. No. 53,684

Date of Deposit: February 23, 2007
This paper or fee is being filed on the date indicated above using the USPTO's electronic filing system EFS-Web, and is addressed to: The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

CANDIS BUENDING
Name

Candis Buending
Signature